Remarks

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Thus, claim 1 has been amended to exclude an acrylic adhesive from the adhesive resin used in the patch of the presently claimed invention. Support for this exclusion is apparent from the disclosure at page 5, lines 4-13 of the specification, indicating that acrylic adhesives are unnecessary in the patch of the present invention.

New claim 4 has been added to the application, and is directed to the adhesive resins disclosed at page 6, lines 21-25 of the specification.

The patentability of the presently claimed invention over the disclosures of the references relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks. [Also please see the Request for Interview submitted concurrently herewith.]

Thus, the rejection of claims 1-3 under 35 U.S.C. §103(a) as being unpatentable over Bracht (US '528) in view of Higo et al. (US '157) is respectfully traversed.

Present Invention

The object of the present invention is to provide a patch containing tulobuterol in a lower concentration, but wherein the patch has controllability of a **stable drug-release**.

This object is achieved by the patch of the present invention, prepared by laminating an adhesive layer consisting of a rubber, a non-acrylic adhesive resin (such as petroleum resin, polyterpene resin, polyolefin resin and saturated alicyclic hydrocarbon resin; see new claim 4), and a plasticizer on a backing, wherein 1 to 4 w/w% of tulobuterol as an active ingredient and 0.1 to 3 w/w% of a higher fatty acid (such as a C_{11-22} fatty acid; see claim 3) **as a drug release controlling agent** are contained in the adhesive layer.

With regard to the permeation of tulobuterol, a patch containing 4% tulobuterol within the scope of present claim 1, is hardly influenced by change in temperature, compared with a patch formulation containing 5% tulobuterol as disclosed in Example 8 in Nakano et al. (US 6,117,447) previously relied on by the Examiner to reject the claims.

References

Bracht discloses a transdermal therapeutic system comprising:

a backing layer,

at least one active substance (tulobuterol hydrochloride)-containing **matrix layer**, and

a removable layer,

wherein the matrix is based (built up) on **polyacrylate pressure-sensitive adhesive** and contains **a polymer having amino-functional group in its side chains**. This preparation (system) is a matrix type preparation containing **polyacrylate pressure-sensitive adhesive** such as Durotak®, and contains **a polymer having amino-functional group in its side chains** such as Eudragit® in a matrix layer.

As an active ingredient, the Bracht preparation contains not tolobuterol, but tulobuterol hydrochloride in the matrix layer, since it has a remarkable advantage compared with the free base.

Bracht discloses that 2-20% of C_{11-22} fatty acid, a rubber (styrene), tackifier and plasticizer may be contained in (the matrix layer of) the system, as indicated by the Examiner, but these substances are only optionally incorporated with essential ingredients, namely **polyacrylate pressure-sensitive adhesive and a polymer having an amino-functional group in its side chains**.

On the other hand, the patch of present invention does not contain these essential ingredients, especially the polyacrylate pressure-sensitive adhesive.

In fact, referring to the disclosure at page 5, lines 4-13 of the present specification, such an adhesive, used in the Bracht preparation, influence the release pattern of tulobuterol and stability with the passage of time.

The Examiner states that Bracht differs from the instant application in that it does not disclose concentrations of rubber, adhesive resin or plasticizer. However, even aside from these differences, Applicants take the position that Bracht does not suggest the patch of the present invention, for the reasons indicated above.

With regard to the Higo et al. reference, as Applicants have previously explained, this reference also discloses a matrix type patch formulation which comprises an adhesive layer containing a physiological active substance (0.1- 20%/0w/w), an organic acid including its water-soluble salt (0.01-15%), a hydrophobic high molecular material (15-60%), a tackifying resin (10- 70%), a plasticizer (10-60%) and an absorption enhancer (0.01-20%). (See column 2, lines 40-52.)

The object of Higo et al.'s invention is to provide a matrix type patch formulation which increases percutaneous absorbability of the physiological active substance and is extremely reduced in irritation to skin where the formulation is applied. (See column 2, lines 24-29.) The reference describes that the inventors "--- found that the percutaneous permeable property of drug is significantly improved --- by formulating a physiological active substance, an organic acid and an absorption enhancer into an adhesive layer---. (See column 2, lines 32-39.)

As explained above, Higo et al.'s invention is characterized by increasing percutaneous permeability of a physiological active substance such as tulobuterol by formulating **an organic acid and an absorption enhancer** into the adhesive layer, i.e. the object of the reference invention is attained by using **a combination of an organic acid and an absorption enhancer**.

As shown in Comparative Examples 1-13 in Higo et al., the objective and desired effect of the reference is not attained by using **either** an organic acid such as sodium propionate (C. Ex. 7, 11, 13), sodium acetate (C. Ex. 8, 10, 12) and sodium salicylate (C. Ex. 9) **or** an absorption enhancer such as pirotiodecane (C. Ex. 1, 2, 3), 1-menthol (C. Ex. 4, 5) and lauryl alcohol (C. Ex. 6) **alone**. Namely, to use either one alone is clearly excluded from Higo et al.'s invention. A higher fatty acid such as C_{11-20} fatty acid is illustrated as one of various absorption enhancers of a physiological active substance therein, but such acid is not used singly or in a combination of the organic acid or its salt in any working examples thereof.

As mentioned above, the present invention is clearly different from Higo et al. in both the problem to be solved and the means for solving the problem.

There is absolutely no suggestion in the Higo et al. reference which would lead one of ordinary skill in the art to use a higher fatty acid such as a C_{11-22} fatty acid **alone**, instead of **a combination of an organic acid and absorption enhancer** as described in the reference. Nor is there any suggestion in the reference that doing so would result in a patch containing tulobuterol in a lower concentration having stable release controllability. That is, one skilled in the art would not be motivated to use such a fatty acid with the expectation of obtaining an improved patch containing tulobuterol.

Thus, claim 1 of the present application uses the expression "**consisting of**"in describing the components of the adhesive layer. This expression excludes the combination of an organic acid and absorption enhancer required by the Higo et al. reference.

In conclusion, the patch of the presently claimed invention is completely different from the preparation of the Bracht reference in using tulobuterol versus its hydrochloride, and a non-acrylic adhesive versus an acrylic adhesive; and the patch of the present invention is also different from the patch of the Higo et al. reference in that the adhesive layer excludes a combination of an organic acid and an absorption enhancer, both of which are required components in Higo et al. Therefore, even **if** one of ordinary skill in the art were motivated to combine Bracht with Higo et al., the art-skilled would not obtain any suggestion from the references to combine 1 to 4w/w% of tulobuterol, a rubber, a non-acrylic adhesive resin, a higher fatty acid, and a plasticizer into a patch formulation, expecting the excellent effect of controllability of stable drug-release, as in the present invention.

For these reasons, Applicants take the position that the presently claimed invention is clearly patentable over the applied references.

Therefore, in view of the foregoing amendments and remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

Respectfully submitted,

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